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Patentanmeldung Nr. | Patent application No. | Demande de brevet n°

03015502.2

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk

Anmeldung Nr:
Application no.: 03015502.2
Demande no:

Anmeldetag:
Date of filing: 08.07.03
Date de dépôt:

Anmelder/Applicant(s)/Demandeur(s):

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Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se referer à la description.)

Steroid modified chacotrioses

In Anspruch genommene Priorität(en) / Priority(ies) claimed /Priorité(s) revendiquée(s)
Staat/Tag/Aktenzeichen/State/Date/File no./Pays/Date/Numéro de dépôt:

Internationale Patentklassifikation/International Patent Classification/
Classification internationale des brevets:

C07J/

Am Anmeldetag benannte Vertragstaaten/Contracting states designated at date of filing/Etats contractants désignées lors du dépôt:

AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL
PT RO SE SI SK TR LI

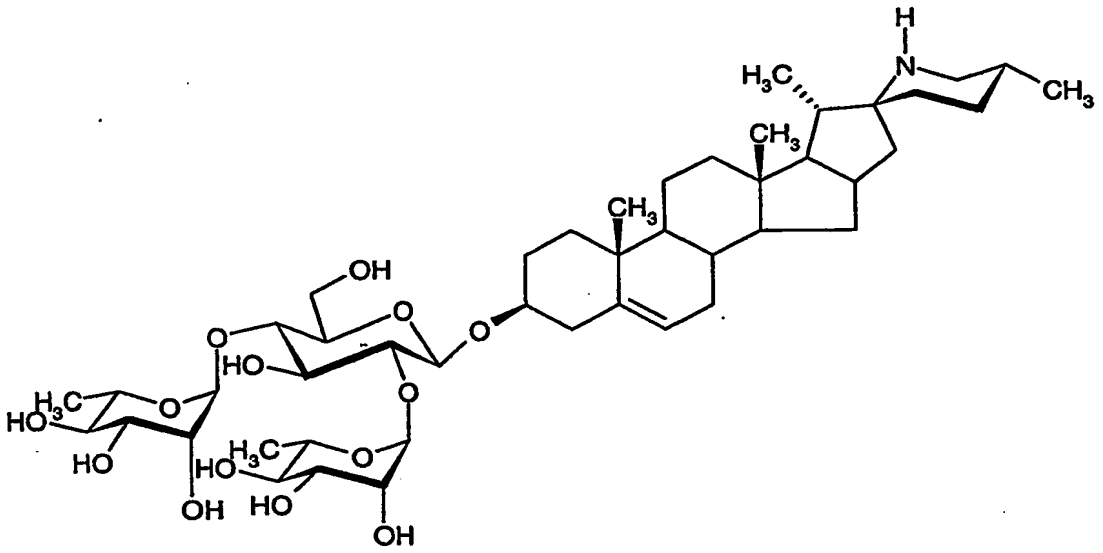
New EP Patent Application
GlycoMed Sciences Limited
Our Ref.: H1874 EP

Steroid modified Chacotrioses

The present invention relates to the chemical synthesis of alkaloid glycosides, in particular to the synthesis of steroid modified chacotrioses. Furthermore, the present invention relates to intermediate compounds useful for the preparation of steroid modified chacotrioses and to novel steroid modified chacotrioses.

Solamargine is a glycoside of the chacotriose type comprising a solasodine steroid unit. Solasodine and its glycosides are of considerable interest commercially and clinically. They are widely used as starting products for the synthesis of various steroidal drugs. The aglycon solasodine is a source for synthetic cortisone and progesterone.

It is moreover well established that certain naturally occurring conjugate solasodine glycosides have potent antineoplastic properties. Of particular interest is the triglycoside solamargine (22R, 25R)-spiro-5-en-3β-yl-α-L-rhamnopyranosyl-(1->2 glu)-α-L-rhamnopyranosyl- (1->4 glu)-β-D-gluco-pyranose. The structure of this triglycoside is as follows:



Solamargine

The above triglycoside is conventionally obtained by extraction from a plant source. A commercially available extract of *S. sodomaeum*, commonly referred to as BEC (Drug Future, 1988, vol. 13.8, pages 714-716) is a crude mixture of solamargine, solasonine (a solatriose derivative of solasodine) and their isomeric diglycosides. The extraction process for making BEC involves homogenizing the fruits of *S. sodomaeum* in a large volume of acetic acid, filtering off the liquid through muslin followed by precipitation of the glycosides with ammonia (Drugs of today (1990), Vol. 26 No. 1, p. 55-58, cancer letters (1991), Vol. 59, p. 183-192). The yield of the solasodine glycoside mixture is very low (approx. 1%). Moreover the individual process steps are not defined to GMP in terms of scale up, definition of yield, composition and product quality.

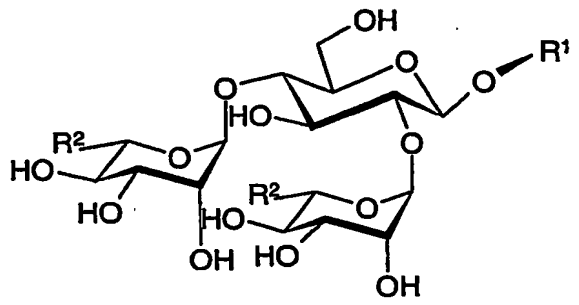
There is a great need for a cost efficient process that provides the antineoplastically active triglycosides such as solamargine and analogues thereof at high yield with little or no impurities.

Contrary to other steroid ring systems, the steroid skeleton of solasodine contains a very labile nitrogen-containing ring. The same hold true for the steroid ring systems of other alkaloids, notably tomatidine, demissidine or solanidine. These aglycons cannot readily be chemically modified while keeping the steroid skeleton intact. In spite of the fact that the aglycon solasodine is readily available, the prior art does not disclose the synthesis of the solamargine using the aglycon as starting material.

The problem underlying the present invention is to provide a cost effective method for the preparation of steroid modified chacotrioses such as solamargine or solamargine analogues in high yields.

Such compounds exhibit cytotoxic activity and may be employed as anticancer agents. Furthermore, such compounds exhibit anti bacterial, anti fungal or anti viral activity.

Accordingly, the present invention provides a process for the preparation of a steroid modified chacotriose of general formula (I):

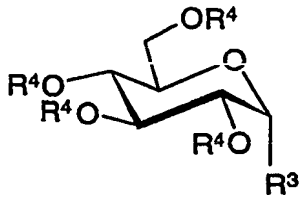


Formula (I)

wherein R^1 represents a steroid or a derivative thereof having a hydroxyl group in the 3-position and no further unprotected hydroxyl groups; and each R^2 independently represents a straight or branched C_{1-14} alkyl group, a C_{5-12} aryl or heteroaryl group optionally substituted by one or more halogen atoms or C_{1-4} alkyl groups, or a hydroxyl group; whereby the C_{1-14} alkyl groups are preferably selected from methyl, ethyl and propyl; the aryl groups are preferably selected from phenyl, p-methylphenyl and p-chlorophenyl; the heteroaryl groups are preferably selected from pyridinyl, pyrimidinyl, furanyl, pyrrolyl, thiophenyl, indolyl, pyrazolyl and imidazolylmethyl; methyl, ethyl and propyl are more preferred. In a particular preferred embodiment R^2 represents methyl.

The method of the present application comprises the step of:

(A) reacting a compound of general formula (II):

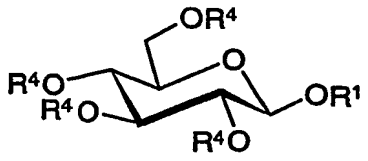


Formula (II)

wherein R^3 represents a halogen atom, an ethylsulfide or a phenyl sulfide group; and each R^4 independently represents a protecting group such as a benzoyl, acetyl or pivolyl group;
with a compound of general formula (III):

$$HO–R^1 \qquad (III)$$

wherein R^1 is defined as above;
to yield a compound of general formula (IV):



Formula (IV)

wherein R^1 and R^4 are defined as above.

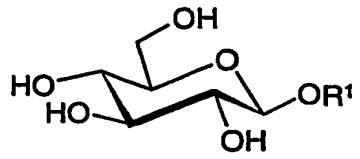
The compound of the above general formula (IV) may be transformed to the desired steroid modified chacotriose of general formula (I) by any suitable method known in the art. A particular preferred procedure is described in detail below.

Furthermore, the present application provides steroid modified chacotriose compounds of general formula (I) as defined above, wherein R^1 represents a tomatidin-3-yl, demissidin-3-yl group, solanidin-3-yl or solasodin-3-yl group.

A further object of the present application is the provision of intermediate compounds useful for the synthesis of the steroid modified chacotriose of general formula (I) defined above, namely:

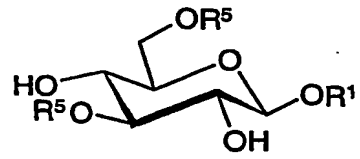
A compound of general formula (IV) as defined above;

A compound of general formula (V):



Formula (V)

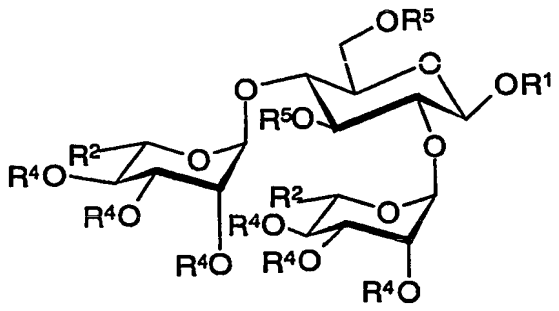
wherein R^1 is defined as above;A compound of general formula (VI):



Formula (VI)

wherein R^1 is as defined above, and R^5 represents a pivolyl protecting group.

A compound of general formula (VIII):



Formula (VIII)

wherein R^1, R^2, R^4 and R^5 are as defined above.

Further embodiments of the present application are described in the dependent claims.

Detailed description of the invention

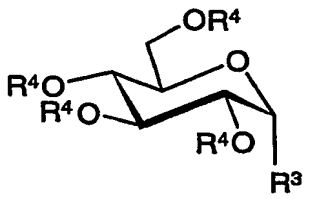
In the following, the present invention will be explained in more detail with reference to preferred embodiments.

The steroid residue constituting substituent R^1 is a steroid or a derivative thereof having a hydroxyl group in the 3-position that serves as the α-glycosidic hydroxyl group, which binds the steroid residue to the compound of formula (II) defined above. The steroid residue bears no further unprotected hydroxyl groups and preferably has no further hydroxyl groups at all, in order not to compromise subsequent reaction steps. In a preferred embodiment of the present invention R^1 is selected from a tomatidin-3-yl, demissidin-3-yl, solanidin-3-yl and solasodin-3-yl group.

All of those steroid groups contain a labile nitrogen-containing ring and, therefore, cannot be chemically modified by means of conventional methods. Moreover, all of the above steroid groups represent substituents for cyctotoxic, anti bacterial, anti fungal or anti viral compounds.

In the above general formula (I) each R^2 independently represents a straight or branched C_{1-14} alkyl group, a C_{5-12} aryl or heteroaryl group optionally substituted by one or more halogen atoms or C_{1-4} alkyl groups, or a hydroxyl group. In a preferred embodiment R^2 represents a C_{1-14} alkyl group selected from methyl, ethyl and propyl; an aryl group selected from phenyl, p-methylphenyl and p-chlorophenyl; or an heteroaryl group selected from pyridinyl, pyrimidinyl, furanyl, pyrrolyl, thiophenyl, indolyl, pyrazolyl and imidazolylmethyl; methyl, ethyl and propyl are more preferred.
In a particular preferred embodiment R^2 represents a methyl group.

In step (A) of the method of the present application, a compound of general formula (II):



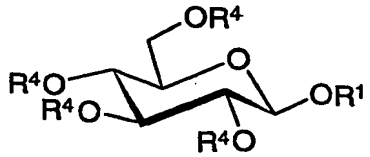
Formula (II)

is reacted with a compound of general formula (III):

$HO–R^1$

Formula (III)

to yield a compound of general formula (IV):



Formula (IV)

In the above general formula (II) R^3 represents a halogen atom, an ethylsulfide or a phenyl sulfide group. Preferably, R^3 represents a bromine atom or a chlorine atom. Most preferably R^3 is a bromine atom. Furthermore, in general formulae (II) and (IV), each R^4 independently represents a benzoyl, acetyl or pivolyl protecting group, preferably a benzoyl protecting group.

Step (A) is preferably conducted in an inert organic solvent such dichloromethane, tetrahydrofuran or dichloroethane. A preferred solvent is dichloromethane.

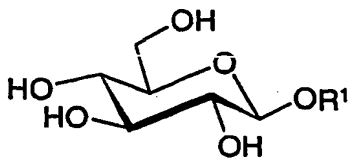
Preferably the reaction is carried out in the presence of a promoter. Any conventional promoter used in carbohydrate chemistry may be employed. Particular preferred promoters include silver triflate, boron trifluoride diethyl etherate (-10°C), trimethylsilyl triflate bromide, N-iodosuccinimide and dimethyl thiomethyl sulfonium triflate. The most preferred promoter is silver triflate.

The reaction may preferably be carried out under anhydrous conditions in the presence of a water detracting means such as 4Å mol sieves.

In a preferred embodiment the reaction is carried out at low temperature such as 0°C or lower, more preferably –10°C or lower. The most preferred reaction temperature is –20°C.

Subsequently, the above-obtained compound of general formula (IV) may be further modified as described below.

In a preferred embodiment of the method of the present application, the compound of general formula (IV) is deprotected in step (B) by removing substituent R^4 to obtain a compound of general formula (V):

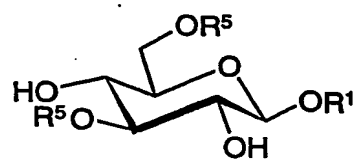


Formula (V)

wherein R^1 is defined as above.

Any suitable deprotection condition conventionally employed in the chemistry of protecting groups may be used. Deprotection is preferably carried out in an inert organic solvent such as dichloromethane or tetrahydrofuran in the presence of an alkali metal alkoxide having 1 to 4 carbon atoms and a C_{1-4} alcohol, or in the presence of water, an alkali metal hydroxide and a C_{1-4} alcohol. In a particular preferred embodiment deprotection in step (B) is carried out in dichloromethane in the presence of methanol and sodium methoxide.

The thus obtained compound of general formula (V) may be selectively protected in 3-OH and 6-OH position using pivolyl chloride in the presence of an amine base to yield compound of general formula (VI):

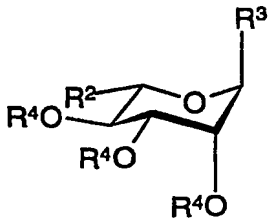


Formula (VI)

wherein R^1 is as defined above, and R^5 represents a pivolyl group. Suitable amine bases include pyridine, triethylamine, collidine, or lutidine. A preferred amine base is pyridine.

The reaction may be carried out in an inert organic solvent. Examples of suitable solvents include tetrahydrofuran, dichloroethane, or dimethylformamide.

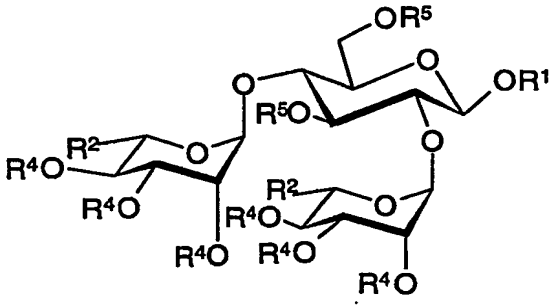
The compound of formula (VI) may be then reacted in step (D) with a compound of general formula (VII):



Formula (VII)

under substantially the same conditions as described above for step (A). In general formula (VII) R^2, R^3 and R^4 are as defined above.

Resulting compound of general formula (VIII):

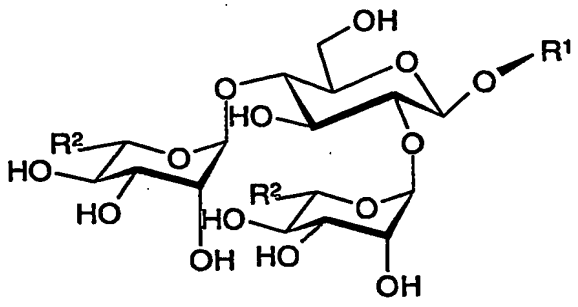


Formula (VIII)

wherein R^1, R^2, R^4 and R^5 are as defined above, may be subsequently deprotected in step (E) to yield the compound of general formula (I) under substantially the same conditions as described above for step (B). In a preferred embodiment step (E) is carried out in tetrahydrofuran in the presence of water, sodium hydroxide and methanol.

Claims

1. A method for the preparation of a steroid modified chacotriose of general formula (I):



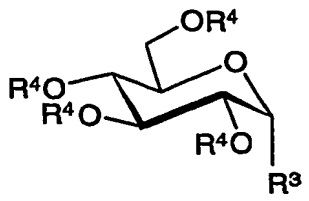
Formula (I)

wherein R^1 represents a steroid or a derivative thereof having a hydroxyl group in the 3-position and no further unprotected hydroxyl groups; and each R^2 independently represents a straight or branched C_{1-14} alkyl group, a C_{5-12} aryl or heteroaryl group optionally substituted by one or more halogen atoms or C_{1-4} alkyl groups, or a hydroxyl group,

which method comprises the step of:

(A) reacting a compound of general formula (II):

(B)



Formula (II)

wherein R^3 represents a halogen atom, an ethylsulfide or a phenyl sulfide group; and each R^4 independently represents a benzoyi, acetyi or pivolyl protecting group;

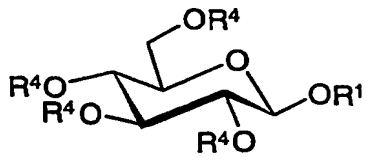
with a compound of general formula (III):

$$HO–R^1$$

Formula (III)

wherein R^1 is defined as above;

to yield a compound of general formula (IV):

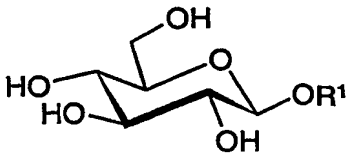


Formula (IV)

wherein R^1 and R^4 are defined as above.

2. The method according to claim 1, further comprising the step of:

(B) deprotecting the compound of general formula (IV) as defined in claim 1 to yield a compound of general formula (V):

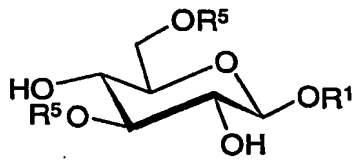


Formula (V)

wherein R^1 is as defined in claim 1.

3. The method according to claim 1 or 2, further comprising the step of:

(C) reacting the compound of general formula (V) as defined in claim 2 with pivolyl chloride in the presence of an amine base to yield a compound of general formula (VI):

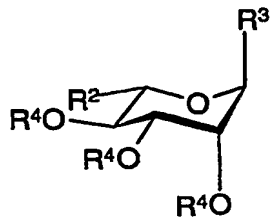


Formula (VI)

wherein R^1 is as defined in claim 1, and R^5 represents a pivolyl protecting group.

4. The method according to any of claims 1 to 3, further comprising the step of:

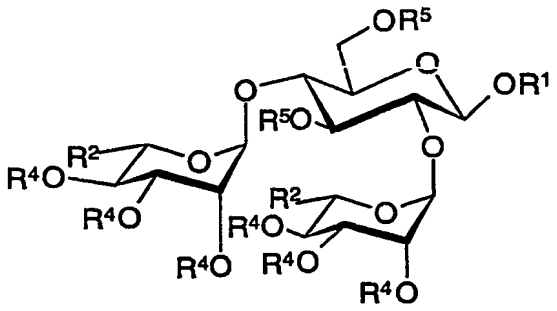
(D) reacting the compound of general formula (VI) as defined in claim 3 with a compound of general formula (VII):



Formula (VII)

wherein R^2, R^3 and R^4 are as defined in claim 1;

to yield a compound general formula (VIII):



Formula (VIII)

wherein R^1, R^2 and R^4 are as defined in claim 1, and R^5 is as defined in claim 3.

5. The method according of any of claims 1 to 4, further comprising the step of:
(E) deprotecting the compound of general formula (VIII) as defined in claim 4 to yield the compound of general formula (I).

6. The method according to any of claims 1 to 5, wherein R^1 represents a tomatidin-3-yl, demissidin-3-yl, solanidin-3-yl and solasodin-3-yl group.

7. The method according to any of claims 1 to 6, wherein R^2 represents a methyl group.

8. The method according to any of claims 1 to 7, wherein R^3 in the compounds of general formula (II) and/or general formula (VII) represents a bromine atom.

9. The method according to any of claims 1 to 8, wherein step (A) and/or step (D) are carried out in the presence of a promoter.

10. The method according to claim 9, wherein the promoter is selected from the group consisting of silver triflate, boron trifluoride diethyl etherate,

trimethylsilyl triflate bromide, N-iodosuccinimide and dimethyl thiomethyl sulfonium triflate.

11. The method according to claim 10, wherein the promoter is silver triflate.

12. The method according to any of claims 1 to 11, wherein step (A) and/or step (D) are carried out under anhydrous conditions in the presence of 4Å mol sieves.

13. The method according to any of claims 2 to 12, wherein step (B) and/or step (E) are carried out in dichloromethane or tetrahydrofuran in the presence of a C_{1-4} alcohol and an alkali metal alkoxide having 1 to 4 carbon atoms.

14. The method according to claim 13, wherein step (B) is carried out in dichloromethane in the presence of methanol and sodium methoxide.

15. The method according to any of claims 2 to 15, wherein step (B) and/or step (E) are carried out in dichloromethane or tetrahydrofuran in the presence of water, an alkali metal hydroxide and a C_{1-4} alcohol.

16. The method according to claim 15, wherein step (E) is carried out in tetrahydrofuran, and wherein the alkali metal hydroxide is sodium hydroxide and the alcohol is methanol.

17. A steroid modified chacotriose of general formula (I) as defined in claim 1 or 7, wherein R^1 represents a tomatidin-3-yl or demissidin-3-yl group.

18. A compound of general formula (VIII) as defined in any of claims 4, 6 or 7.

19. A compound of general formula (VI) as defined in any of claims 3, 6 and 7.

20. A compound of general formula (V) as defined in any of claims 2, 6 and 7.

21. A compound of general formula (IV) as defined in any of claims 1, 6 and 7.

Abstract

The present invention relates to steroid modified chacotrioses and the synthesis thereof as well as to intermediate compounds useful for the synthesis of the steroid modified chacotrioses.